Review Article

Features of Digoxin Toxicity in Atrial Fibrillation and Congestive Heart Failure Patients: A Systematic Review

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Abstract

Digoxin is a cardiac glycoside indicated for the treatment of congestive heart failure, atrial fibrillation or flutter, and certain cardiac arrhythmias. The use of digoxin is limited due to its narrow therapeutic index nature. In high concentrations, digoxin has been associated with toxicity features such as gastrointestinal symptoms, visual effects, and cardiac arrhythmia. This systematic review aims to summarize cases of digoxin toxicity including the risk factors, possible drug-drug interaction with digoxin, and presenting symptoms. A literature search was conducted through PUBMED and Ovid Medline using the keywords "digoxin" and "toxicity". The clinical and laboratory manifestations associated with digoxin toxicity were also noted in this review. The search generated 2399 articles and only 10 articles were included in the final analysis. Four out of 10 cases reported diuretics as a possible interacting medication. The symptoms that were usually reported in most cases were nausea and vomiting, change in vision, bradycardia, and increased serum digoxin level. The main risk factors that could lead to digoxin toxicity were females, elderly (60-91 years old), drug-drug interaction; and renal problems (renal disease/ renal impairment/ renal insufficiency). Digoxin toxicity could occur in either low or normal levels of serum digoxin concentration with the presence of concomitant drugs or could be influenced by underlying risk factors. The most common presenting symptoms of digoxin toxicity included nausea and vomiting, change in vision, and bradycardia.

Keywords: Digoxin, Toxicity, Heart failure, Atrial fibrillation

Introduction

Cardiac glycosides, including digitalis and digoxin, have long-standing use in clinical practice [1]. Digoxin is indicated in patients with heart failure (HF) and impaired systolic function who are in sinus rhythm and continue to have signs and symptoms despite standard therapy that includes angiotensin-converting enzyme inhibitors and beta-blockers. Digoxin may also be particularly useful in patients with severe symptoms, left ventricular ejection fraction (LVEF) less than 25%, or cardiomegaly on chest x-ray. Digoxin is also indicated in patients with atrial fibrillation, with or without HF, and a rapid ventricular response [2].

Digoxin is a cardiac glycoside with positive inotropic characteristics. It works by inhibiting the sodium-potassium adenosine triphosphatase (ATPase) pump at the cellular level and prevents the transport of sodium from the intracellular to the extracellular space [3]. In addition, digoxin also has effects on the autonomic nervous system. It has parasympathomimetic actions that clinically manifest by increasing vagal tone to the sinus and atrioventricular (AV) nodes, thus decreasing heart rate and slowing conduction through the AV node. In patients with heart failure, digoxin has anti-sympathetic effects, including restoration of baroreceptor sensitivity (which is decreased in low-output heart failure). The exact underlying mechanism for these effects remains unclear but the sympatholytic actions first appear at relatively low digoxin concentrations – below those needed to cause a measurable increase in the force of contraction [4]. Although considered generally safe, several recent studies have reported digoxin to have potential proarrhythmic properties, long-term effects on cardiac remodeling, and even link to adverse prognosis in atrial fibrillation (AF) [5].

Digoxin has a narrow therapeutic window so it can easily reach toxic levels in the body. As a result, digoxin users should be closely monitored for adverse effects and the serum level need to be kept within therapeutic range to prevent the

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increased risk of digoxin-associated mortality [6]. The common symptoms may be mild and include nausea, vomiting, and anorexia. It can also cause visual side effects that include color changes, also known as xanthopsia. However, yellow or green-tinted vision is usually associated with digoxin toxicity. Besides, patients may also highlight blurry vision or photopsia. At toxic levels, digoxin is proarrhythmic. An impaired ventricle is more prone to ventricular tachyarrhythmias and ectopy. Abnormally high levels of digoxin will stimulate atrial activation, thus atrial tachycardias, which, in a patient on digoxin, is highly suggestive of toxicity. These atrial tachycardias are persistent and resolve with a decrease in serum digoxin levels. Other common side effects include rash, headache, gynecomastia, and weakness [1].

This systematic review aims to provide a detailed analysis of the currently available case reports related to digoxin toxicity. It also aims to investigate the clinical and lab manifestations including potential risk factors presented leading to digoxin toxicity (e.g.: renal impairment or drug-drug interaction (DDIs)).

Materials and Methods

Data Sources and Searches

Articles published in PubMed and Ovid were systematically searched using the keywords "digoxin" and "toxicity". The search covered all case studies published until 2020.

Study Selection

The titles and the abstracts were screened based on the following inclusion criteria:

a. Case reports (the presenting symptoms and risk factors observed were based on real settings);
b. Involved human;
c. Published in English or translated study in English;
d. Described the dose of digoxin used, possible interacting drugs with digoxin, risk factors, and presenting symptoms of digoxin toxicity

Studies related to digoxin-herbal medicine interaction were excluded. The selected articles were later screened based on the full-text content and any redundancy was removed.

Data Extraction and Data Synthesis

A detailed review of full-text articles was conducted and relevant information in each of the articles was identified. The articles were categorized according to their topic relevance and the extraction of data includes:

a. Reference information: author, year of publication, and source of the journal;
b. Patient information: age, gender;
c. Characteristics of digoxin therapy: the dose of digoxin use, the purpose of the use, duration of digoxin therapy;
d. Possible cause of digoxin toxicity: exposure to digoxin monotherapy, potential interacting drugs with digoxin;
e. Case presentation: medical history, the clinical manifestation of digoxin toxicity, heart profile (ECG diagram), and digoxin concentration level; and
f. Risk factors of the occurrence of digoxin toxicity: advanced age, female gender, drug-drug interactions, renal impairment or insufficiency condition, loose communication between health practitioners, lack of knowledge on plants recognition

All data analyzed were presented as a descriptive summary of the studies and results. No additional statistical analysis was performed.

Assessment of Study Quality

Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used for case reports to assess the quality of studies. The tool consists of eight domains including:

a. The patient's demographic characteristics;
b. The patient's history timeline;
c. The current clinical condition of the patient on presentation;
d. Description of diagnostics tests or assessment methods and the results;
e. Description of intervention or treatment procedure;
f. Description of post-intervention clinical condition;
g. Identification and description of adverse events (harms) and/or unanticipated events;
h. Provide takeaway lessons.

Each domain was considered for each of the studies included and overall appraisal determined whether the study would be included or excluded from the systematic review.

Data Analysis

All data gathered were summarized in tables according to the topic of relevance. The summarized data were analyzed and discussed qualitatively.

Results and Discussion

A total of 2399 articles were generated from both PubMed and Ovid searches (1827 and 572, respectively). "Case report" was included in the search filter. Further searches were performed using the inclusion criteria such as human studies in English languages. All articles related to drug toxicity induced by factors other than digoxin treatment were excluded. Based on these features, 80 potentially relevant articles were obtained in this study.

Upon further screening, 63 articles were removed due to duplication and accessibility issues. The remaining articles were appraised for eligibility. Nine articles were excluded since detailed information from the full-text screening indicated that the case involved false-elevation of digoxin levels induced by plants and other cases of drug toxicity that were unrelated to the ingestion of digoxin. In total, 8 articles on digoxin-induced toxicity were included in this systematic review.

Study Eligibility

All case reports presented in this study were reported in complete detail as recommended by the eight domains listed in the (JBI) Critical Appraisal Checklist. A total of 10 eligible case reports were included in this study.

Use and Dosage of Digoxin

Digoxin is a type of medicine known as a cardiac glycoside that was commonly used to manage arrhythmias including atrial fibrillation. It is also indicated in the management of symptoms associated with congestive heart failure, usually in combination with other medications.

There were four cases (50%) reported the use of digoxin to treat atrial fibrillation [7-10], one case for the treatment of congestive heart failure (CHF) only [11], and one case for the treatment of both clinical conditions [12]. Digoxin had also been used for the treatment of dilated cardiomyopathy with Left Ventricular Ejection Fraction (LVEF) [13] and paroxysmal supraventricular tachycardia [14].

The dosage prescribed in four of the cases (50%) was 0.25 mg daily [7, 8, 10, 12] while 0.125 mg dosage was reported in 2 cases [9, 11].

Drug-Drug Interaction with Digoxin

There were 2 cases of digoxin toxicity that were not related to any possible drug-drug interaction [8, 9]. The remaining six cases had several possible interacting drugs which were likely to interfere with the mechanisms of digoxin and eventually lead to the occurrence of digoxin toxicity.

Diuretics were the most reported possible interacting drug in four cases. One of them had caused drug-drug interaction [12] and another three cases were classified as potential to cause digoxin-diuretic interaction [11, 13, 14]. The possible interacting diuretics reported in three cases involved Furosemide, which is a loop diuretic, and Spironolactone, which belongs to potassium-sparing diuretics [11-13]. One case reported the digoxin-diuretic interaction without indicating the specific agent [14].

Another frequently reported possible interacting drug was Diltiazem, which was reported in 2 cases of digoxin toxicity [7, 11]. Renard *et al*. 2015, stated that the digoxin-diltiazem interaction was most probably caused by the increased exposure to digoxin through uncertain mechanisms, possibly by inhibiting P-glycoprotein, while in the case of Yang *et al*. 2012 diltiazem was discontinued due to high clinical suspicion for digoxin toxicity. Besides Diltiazem, other atrioventricular nodal blocking agents such as Carvedilol may also cause possible drug-drug interaction with digoxin [11].

Other medications with the possibility to induce digoxin-drug interaction were Dronedarone (antiarrhythmic drug) [10], Celecoxib (NSAIDs), and Levothyroxine (antithyroid) [12]. Renard *et al*. 2015 also reported that Torsemide and Lisinopril could aggravate renal failure, risk of dehydration, and electrolyte imbalance which eventually lead to digoxin toxicity.

Presenting Symptoms of Digoxin Toxicity

The main presenting symptoms associated with toxicity that were mostly observed in these case reports were nausea and vomiting. The important laboratory result to determine the presence of digoxin toxicity was the serum digoxin level which the normal range is between 0.8 – 2.0 ng/ml.

Most of the cases reported the presence of nausea and vomiting associated with increased digoxin levels. Other symptoms of digoxin toxicity such as a visual change, visual disturbance (snowy and blurry vision), and visual hallucination were observed in four cases. Visual disturbances described as flashing lights and yellow or red halos around the object were observed in 1 case [14]. Snowy and blurry vision was reported by Renard *et al*. [7] while the change in vision with the disappearance of color vision was reported by Kolev [8]. Visual hallucinations were also reported by Naha *et al*. [14].

The occurrence of bradycardia was also observed in a total of three case reports [10, 11, 14]. In addition, one case reported the presence of weakness, fatigue [11], and lethargy [8], respectively. Other symptoms reported to be associated with digoxin toxicity were reduced level of consciousness [12], palpitation, chest discomfort, dysphagia [7], complete atrioventricular heart block [11], and loss of appetite [8].

The majority of the cases reported the value of serum digoxin level (SDL) higher than the cut-off point of 2.0 ng/ml [7, 9-11, 13, 14].

Table 1. Presenting symptoms of digoxin toxicity.

Author (Year)	Dose (mg/day)	Presenting symptoms				Serum Digoxin level Normal: 0.8-2.0 ng/mL
		Nausea & Vomiting	Change in vision	Bradycardia	Other symptoms	
[7]	0.25	/	-Snowy and blurry vision		Dysphagia	5.7
[8]	0.25	/	The disappearance of color vision		-Lethargy -Loss of appetite -Slow AF:35-38 bpm	-

[9]	0.125				Ventricular fibrillation following bidirectional tachycardia	2.4
[10]	0.75			Junctional bradycardia	Dizziness	>5
[11]	0.125			/	-Recurrent episode of syncope associated with coughing - Increasing weakness -Dyspnoea -Become nonresponsive -Complete atrioventricular heart block showed by electrocardiogram (ECG)	4.3
[12]	0.25	/			-Increasing confusion -Reduced level of consciousness	3.0
[13]	Not stated	/				2.5
[14]	Not stated	Recurrent vomiting for 3 days	-Photophobia -Visual hallucination -Yellow vision		-Condition persisted although symptomatic treatment with antiemetics	3.63

Risk Factors of Digoxin Toxicity

They were four main possible risk factors that may be associated with digoxin toxicity: being female; elderly (60-91 years old); the presence of drug-drug interaction; and having a renal problem (renal disease/ renal impairment/ renal insufficiency). Most of the digoxin toxicity cases presented had at least one or more risk factors of digoxin toxicity. Other factors discussed in the case reports included hypomagnesemia, hypothyroidism, polypharmacy with questionable adherence, and loose communication between the cardiologist and general practitioner (GP). All the risk factors were summarized in the table below:

Table 2. Risk factors of digoxin toxicity

Author	Dose (mg)	Risk factors				
		Female	Advanced age (years)	Drug-drug interaction	Renal problem	Others
[7]	0.25	/	91	Diltiazem, Torsemide, Lisinopril	Pre-existing advanced kidney disease	Polymedication with questionable
[8]	0.25	/	76		Impaired renal functions	
[9]	0.125	/	79			
[10]	0.75	/	82	Dronedarone		Hypomagnesemia
[11]	0.125		73	AV nodal blocking agents: carvedilol, diltiazem	Chronic renal insufficiency	
[12]	0.25	/	69	Celecoxib, Furosemide, Levothyroxine, Spironolactone	An acute episode of renal impairment	Hypothyroidism
[13]		/	30	Furosemide		
[14]		/	65	Diuretics		

Use and Dosage of Digoxin

The two main indications for digoxin identified based on this review were congestive heart failure and atrial fibrillation. In heart failure patients, digoxin demonstrated its inotropic properties by inhibiting the sodium-potassium ATPase which leads to increased intracellular calcium concentrations through the sodium-calcium exchanger. This would cause the cardiac action potential to lengthen which caused lower heart rates as well as increased myocardial contractility due to the increased calcium for sarcomeric excitation-contraction coupling [15]. Another mechanism of digoxin was via AV Node Inhibition. Digoxin had vagomimetic effects on the AV node. By stimulating the parasympathetic nervous system, it slowed electrical conduction in the atrioventricular node,

therefore decreasing the heart rate. The raised in calcium levels leads to the prolongation of phase 4, and phase 0 of the cardiac action potential and thus increasing the refractory period of the AV node. Slower conduction through the AV node resulted in a decreased ventricular response [1].

Digoxin was on the list of high-alert medications because of its narrow therapeutic range and high drug-drug interactions (DDIs) potential. Concentration changes of digoxin in the body were related to factors such as physiological characteristics, disease state, and co-administered drugs. Inappropriate doses may lead to excessive drug concentrations in the body and thus cause numerous adverse reactions that affect the functioning of multiple organs [16]. Oral digoxin was available as a solution (0.05 mg/mL) or as tablets (0.0625 mg, 0.125 mg, and 0.25 mg). Dosing should be initiated and maintained at doses of 0.125 to 0.25 mg daily, with lower doses considered in patients 70 years of age or older [12].

In atrial fibrillation, serum digoxin concentration is usually targeted higher at 1-2 ng/ml. For heart failure, the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 ng/ml to 0.5–0.9 ng/ml. This is because of evidence of better outcomes at lower concentrations. The serum digoxin concentration does predict the likelihood of toxicity. Nevertheless, digoxin toxicity could also occur even when the serum digoxin concentration is within the therapeutic range [17].

Drug-Drug Interaction with Digoxin

Six out of 10 cases (60%) reported the actual occurrence of digoxin toxicity which was caused by drug-drug interaction (DDIs). The highest possible interacting drug with digoxin in this review is diuretics medications. Diuretics are considered currently to be the first-line treatment for patients with chronic heart failure, irrespective of etiology, age, sex, and individual characteristics of the patient since they can relieve symptoms quickly and control fluid retention [18]. Examples of diuretics that were found to have an interaction with digoxin in this review were Furosemide and Spironolactone [11-13].

Electrolyte disturbance is believed to be the main mechanism responsible for the digoxin–diuretic interactions and the use of diuretics including thiazides and loop diuretics has been found to cause potassium or magnesium deficit [19]. Besides, potassium-sparing diuretic drugs such as spironolactone have been reported to induce changes in digoxin's pharmacokinetics. It will increase the plasma concentration of digoxin by inhibiting tubular secretion. As a result, renal clearance and extrarenal clearance of digoxin will be reduced [20].

Another possible interacting drug that was found in this study was Diltiazem, although the exact mechanism was uncertain; possibly by inhibiting P-glycoprotein (P-GP) [7]. P-glycoprotein is an energy-dependent efflux transporter. It pumps drug molecules out of cells. P-GP is found in the epithelial cells of the intestine (enterocytes) along the apical (luminal) side of the cell. When a drug is taken orally, drug molecules have to pass through the enterocyte to enter the blood. As the molecules diffuse through the enterocyte, P-GP can pick up the molecules and carry them back to the luminal side of the cell, where they are redeposited into the lumen of the intestine. This action prevents drug molecules from reaching systemic circulation, effectively limiting bioavailability. If the activity of P-GP is inhibited, more drugs will be absorbed through the enterocytes, and plasma concentrations will be increased [21].

Other findings also showed that digoxin may interact with Levothyroxine which is one of the thyroid hormone medications. This is because the clearance of or sensitivity to digitalis glycosides may be increased in previously hypothyroid patients when a euthyroid state is achieved after the addition of thyroid hormones. As a result, the patient needs to be monitored closely for altered efficacy and safety while achieving a euthyroid state or when thyroid hormones are added, discontinued, or dosing changes are made [22]. On the contrary, Dronedarone increases digoxin concentration by P-glycoprotein interaction. Lisinopril may increase the blood levels and effects of digoxin, while Torsemide will reduce the level of potassium in the blood subsequently increasing the effects of digoxin in the body.

Presenting Symptoms of Digoxin Toxicity

Seven out of 10 cases reported digoxin toxicity manifested as gastrointestinal symptoms; nausea and vomiting (70%) as the most commonly presenting symptoms. Four out of the seven cases were associated with elevated serum digoxin levels, which is higher than the normal range of 0.8 -2.0 ng/ml. Other accompanied clinical symptoms include a change in vision and the occurrence of bradycardia. Examples of change in vision in these case reports were visual disturbances presented with flashing lights and yellow or red halos around the object observed, the disappearance of color vision, and the appearance of visual hallucination.

Risk Factors of Digoxin Toxicity

Digoxin toxicity may be influenced by several patient risk factors such as hypothyroidism, advanced age, and renal insufficiency [23]. The majority of cases reported in our review suggested that underlying renal or kidney problems could lead to the occurrence of digoxin toxicity. Reduced kidney function caused the accumulation of digoxin in the blood due to reduced elimination. A study found that nearly half of the patients with digoxin toxicity were suffering from renal impairment. Therefore, digoxin blood levels need to be monitored frequently in this population, especially for the elderly [24].

Another risk factor that was associated with digoxin toxicity is advanced age. The age of patients reported in these cases ranged from 30 to 91 years old with an average age of 68 years old. Advanced age might be associated with digoxin

toxicity, as these patient populations tend to be at risk of developing congestive heart failure (CHF) and Atrial Fibrillation (AF). These medical conditions were markedly more prevalent in old age. Besides that, age-related decline in renal function and a decrease in the volume of digoxin distribution could also cause a patient to become more susceptible to digoxin toxicity [25]. Hypothyroidism was also one of the risk factors as thyroid abnormalities could alter digoxin pharmacokinetics. A hypothyroid state reduces both volumes of distribution and clearance while a hyperthyroid state increases both [12]. However, the mechanism of the interaction between sex and digoxin therapy was still unknown.

Conclusion

Digoxin was commonly used to treat congestive heart failure (CHF) and atrial fibrillation (AF) with a dose of 0.125 mg or 0.25 mg. Diuretics were the most commonly reported interacting drugs with digoxin due to several mechanisms. The most common symptoms associated with digoxin toxicity were nausea, vomiting, change in vision, and bradycardia. Risk factors that may be associated with digoxin toxicity include being female; elderly (60-91 years old); having drug-drug interaction; and having renal problems (renal disease/ renal impairment/ renal insufficiency). Serum Digoxin concentration monitoring is highly recommended in these patient populations to ensure drug efficacy and prevent any possible associated toxicity.

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